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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,824	10/23/2003	John Langenfeld	54704.8036.US03 RWJ-01-02	1322

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,824	LANGENFELD, JOHN	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20060712*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 15, 2006, has been entered.

1. The amendment filed July 12, 2006, is acknowledged and has been entered.

2. Claims 1 and 14 are pending in the application and currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The information disclosure filed July 12, 2006, has been considered. An initialed copy is enclosed.

Response to Amendment

5. Applicant's remarks beginning at page 7 of the amendment filed July 12, 2006, which address the issue of the non-responsiveness of the prior amendment filed February 17, 2006, are acknowledged, but considered immaterial since the amendment to the claims filed July 12, 2006, has rendered the issue moot. The present claims are drawn to the invention constructively elected by original presentation for prosecution on the merits.

Priority

6. Applicant's claim for benefit of the earlier filing date of copending U.S. Application No. 10/044,716, filed January 11, 2002, which, in turn, claims benefit of U.S. Provisional Application No. 60/261,252, filed January 12, 2001, is acknowledged.

However, as explained in the preceding Office action, Applicant has not complied with one or more conditions for receiving the benefit of the earlier filing dates of the provisional application under 35 U.S.C. § 120.

To receive benefit of the earlier filing date under 35 USC § 120, the claims must be directed to an invention that is disclosed in the prior application; and that earlier disclosure must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. In this instance, for the reasons addressed herein, the description by the earlier filed application of the invention that is claimed in this application is not deemed sufficient to satisfy these requirements. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The reasons that this application does not properly benefit from the earlier filing date of the copending U.S. Application No. 10/044,716 are set forth in the section 4 of the Office action mailed April 27, 2005. In particular, there is no showing, prophetic or otherwise, that the inhibition of an activity of BMP-2 reduces vascularization of a tumor. Furthermore, there is factual evidence of record that shows that BMP-4, rather than BMP-2, is overexpressed in the tumor cells that were used in the disclosed studies. Moreover, only the instant application describes an antibody that binds specifically to BMP-2 without cross-reacting to BMP-4, such that results described in the prior filed copending application cannot be taken as evidence that BMP-2, as opposed to BMP-4, is overexpressed in the cancer cell lines and lung cancer specimens tested.

Furthermore, the present claims are drawn to a method for reducing vascularization of a BMP-2-overexpressing tumor in a tumor comprising administering to a subject an inhibitor of BMP-2 activity that comprises noggin. Copending U.S. Application No. 10/044,716 does not provide an enabling disclosure of the claimed invention, since it does not teach the effect upon tumor vascularization of administering an inhibitor of BMP-2 activity, which comprises noggin. At paragraph [00142] the

copending application describes an analysis that could be performed to assess the effects upon tumor growth and vascularization in mice by inoculating with lung cancer cells mice in the presence of agarose beads coated with albumin, BMP-2, or noggin, but it does not describe, or even prophesize reduced tumor vascularization in the presence of noggin. Moreover, this disclosure does not adequately describe the claimed invention, as it does not reasonably provide written support for reducing vascularization of a BMP-2-overexpressing tumor in a tumor comprising administering to a subject an inhibitor of BMP-2 activity that comprises noggin.

Therefore, the effective filing date of the instant claims is considered to be the date that the present application was filed, namely October 23, 2003.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments filed July 12, 2006, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed March 3, 2006.

Grounds of Objection and Rejection Maintained

Specification

8. The objection to the specification, because the use of improperly demarcated trademarks, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant has made a *bona fide* attempt to resolve this issue by amending the specification to properly demarcate trademarks, there are still additional examples of improperly demarcated trademarks (e.g., Tween™ (paragraph [0153] and [0187])).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic

terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 112

9. The rejection of claims 1 and 14 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At pages 7-11 of the amendment filed February 17, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant's arguments are predicated, in part, on the expected entry of the proposed amendment to the claims, which was filed February 17, 2006. However, since the amendment to the claims has not been entered, those arguments are presently moot.

At page 8 of the amendment, Applicant has remarked that he disagrees with the Examiner's suggestion that a role for BMP-2 must be established before therapeutic benefit of noggin can be realized, as there is no such requirement set forth under 35 U.S.C. § 112, first paragraph. While perhaps it may be said the statute does not require that a role for BMP-2 must be established before therapeutic benefit of noggin can be realized, it does require a disclosure that reasonably enable the skilled artisan to practice the claimed invention without undue and/or unreasonable experimentation. As the claimed invention is a method for reducing vascularization of a BMP-2 overexpressing lung tumor in a subject by administering to the subject a therapeutically effective amount of an BMP-2 inhibitor comprising noggin, the amount of guidance, direction and exemplification set forth in the specification must be sufficient to enable

the skilled artisan to achieve the claimed objective by practicing the invention, and it must do so without need for further undue and/or unreasonable experimentation.

The position of the Office is that such use of the claimed invention would not be reasonably enabled by the instant specification, as the skilled artisan could not do so without first establishing the role of BMP-2 in lung cancer, determine whether or not its inhibition would be clinically advantageous, and, if so, identifying and making a suitable inhibitor of BMP-2 activity that comprise noggin, such that tumor vascularization is reduced and the patient clinically benefits from the treatment.

Applicant has argued their own publications, which were published in 2003 and 2004, support the disclosure that inhibiting BMP-2 activity reduces vascularization of lung tumors. Without intending to acquiesce, it is aptly noted that such supporting documents published after the filing date sought by Applicant cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See MPEP § 2164.05(a).

Furthermore, contrary to Applicant's assertions, it is submitted that both these publications, i.e., Langenfeld et al. (2003) and Langenfeld et al (2004) (both of record) suggest the amount of guidance, direction and exemplification set forth in the specification would not be sufficient to have enabled the use of the claimed invention as of the filing date sought by Applicant.

As noted in the Office action mailed April 27, 2005, much of that disclosed in the present application has been published. Langenfeld et al. (*Carcinogenesis*. 2003; **24** (9): 1445-1454) teaches that BMP-2, but not BMP-4 is overexpressed in non-small cell lung cancer cells, as compared to normal lung cells or benign tumor cells of the lung; see entire document (e.g., the abstract). Langenfeld et al. shows that ectopic, enforced expression of BMP-2 in a A549 lung cancer cell line enhanced the growth of tumors in nude mice inoculated with these cells; see, e.g., the abstract. Langefeld et al. teaches inhibition of BMP-2 activity by recombinant noggin or an antibody that binds BMP-2 significantly reduced this tumor growth; see, e.g., the abstract. However, as in the disclosed examples, the inhibitors were *co-injected* with the A549 lung cancer cells

(page 1447, column 1). Langenfeld et al. concludes that these data demonstrate that BMP-2 *may* have important biological activity in human lung carcinomas but cautions that "[f]urther studies are needed to define the specific mechanisms activated by BMP-2 in human carcinomas" (page 1453, column 1).

As further noted in the Office action of April 27, 2005, Langenfeld and colleagues have more recently published an additional report (Langenfeld et al., *Molecular Cancer Research.* 2004 Mar; 2: 141-149) that discloses although BMP-2 is highly overexpressed in the majority of patient-derived lung carcinomas, a mechanism revealing its role in cancer has not been established; see entire document (e.g., the abstract). Similarly, Langenfeld et al. disclose that the role of BMP family members in vascular development has not been extensively studied (e.g., page 145, column 1); however, Langenfeld et al. discloses results that they conclude show that inhibition of BMP-2 by noggin or antisense transfection decreases the lung tumor vasculature in their nude mouse model (e.g., page 145, column 2). Thusly, Langenfeld et al. discloses a study that furthers our understanding of the role of BMP-2 in lung cancer; it is however apparent that our understanding is not yet complete (e.g., page 146, column 2, through page 147, column 1). In particular, Langenfeld et al. discloses that while the inhibition of BMP-2 activity by noggin in A549 lung cancer cells appears to inhibit the growth of the tumor in nude mice, other studies have demonstrated quite paradoxically that the inhibition of BMP-2 activity in different types of tumor cells may actually promote their growth (page 147, column 1).

Indeed, there are paradoxical, conflictive results reported in the literature, which indicate the role of BMP-2 in cancer is not well enough understood to permit reasonable use of the claimed invention without first performing additional undue and unreasonable experimentation to establish its role and determine if inhibiting its activity will provide therapeutic benefit to patients diagnosed with cancer.

Tada et al. (of record), for example, have reported that treatment of the same A549 lung cancer cells used by Langenfeld and colleagues in their studies with BMP-2 resulted in *inhibition* of their growth in anchorage-dependent and independent growth conditions; see entire document (e.g., the abstract). Accordingly, the skilled artisan

might reasonably conclude that inhibiting the activity of BMP-2 by, for example, exposing tumor cells to noggin would not be therapeutic, since it would to the contrary be expected that inhibiting BMP-2 might actually promote the growth of the tumor.

Therefore, despite the finding disclosed in the instant application that co-injecting mouse noggin and A549 lung cancer cells slows or reduces the formation and vascularization of tumors in immunocomprised mice, it is disturbing that contacting A549 lung cancer cell line with noggin *in vitro* promotes, rather than inhibits the growth of the cells. Why is it that mouse noggin acts to suppress the growth these cells *in vitro* but when injected into mice together with the cells apparently causes a reduction in their ability to form tumors? It is submitted that such a paradoxical finding is at odds with most, if not all other studies of potential therapeutic agents, since in general an agent that reduces the growth of tumor cells *in vitro* is expected to have the same effect *in vivo*. The finding that noggin has *opposite* effects upon the growth of A549 lung cancer cells *in vitro* and *in vivo* would not be expected. Again, it is because of such incongruous findings that *Langenfeld et al. (2003) and Langenfeld et al (2004) (both of record) suggests* the need for further experimentation before concluding that BMP-2 has a role in the progression, as opposed to the suppression of cancer.

So, just how the opposing conclusions of Langenfeld et al. and Tada et al. might be reconciled is not known, but the need to further clarify the role of BMP-2 in tumorigenesis before practicing the claimed invention is apparent.

Still others have reported that BMP-2 has an inhibitory role, rather than a stimulating role, in lung carcinogenesis. For example, Buckley et al. (of record) have disclosed results that they conclude show that BMP-2 suppresses the transformed phenotype of A549 cells in vitro; see entire document (e.g., the abstract). Similarly, Buckley et al. reports that BMP-4 can induce senescence and thus negatively regulate the growth of A549 lung cancer cells (see, e.g., the abstract). Again, the results published by Buckley et al. would suggest that contrary to the assertions set forth in the instant application, the inhibition of BMP-2 would not be therapeutic.

While Langenfeld and colleagues have concluded that BMP-2 promotes angiogenesis, since, e.g., its inhibition diminished blood vessel formation (Langenfeld et

al. 2004; see, e.g., the abstract), and therefore promotes tumorigenesis, other investigators have posed that BMP-2 has a role in preventing cancer. Hardwick et al. (of record), for example, concludes that BMP-2 acts as a tumor suppressor, since their study shows the protein promotes apoptosis and differentiation and inhibits proliferation of mature colonic epithelial cells; see entire document (e.g., the abstract). In fact, Hardwick et al. discloses that expression of the gene encoding BMP-2 in dysplastic epithelial cells of microadenomas acquired from patients genetically predisposed to colorectal cancer is lost (page 118). Contrary to the presumed utility of administering to a patient diagnosed with cancer an inhibitor of BMP-2 activity, which asserted in this application, Hardwick et al. discloses that administering noggin to mice led to reduced apoptosis of colon cells; see, e.g., page 117, Figure 7. Hardwick et al. concludes, as loss of BMP signaling appears to lead to decreased apoptosis, its loss would be expected to be associated with increased carcinogenesis (page 120). Similarly, Haramis et al. (of record) published the results of a study that they conclude shows that loss of BMP-4 activity leads to colon polyp growth and ultimately neoplasia (i.e., cancer); see entire document (e.g., the abstract). Haramis et al. discloses that inhibiting BMP signaling by noggin results in the formation of cellular structures in the colonic crypts, which mirror those that occur in patients predisposed to cancer by the syndrome juvenile polyposis (e.g., abstract). More recently, Nishanian et al. (of record) teaches that inactivation of BMP signaling by mutation of a BMP receptor actually causes familial juvenile polyposis; see entire document (e.g., the abstract).

In other types of cancer, too, including, for example, breast cancer cells, BMP-2 has been reported to act as an antiproliferative agent. For example, Ghosh-Choudhury et al. (of record) discloses that BMP-2 dose-dependently inhibits the growth of MDA MB 231 human breast cancer cells; see entire document (e.g., the abstract). By way of mechanism, Ghosh-Choudhury et al. discloses that BMP-2 treatment arrests the cells in the G1 phase of the cell cycle, perhaps as a result of causing the hypophosphorylation of the retinoblastoma protein (Rb) and increasing the expression of the tumor suppressor p21 (e.g., abstract). Apparently, BMP-2 also causes hypophosphorylation of Rb and increases expression of p21 in prostate cancer cells, which Tomari et al. (of

record) teaches may explain how BMP-2 inhibits their proliferation; see entire document (e.g., the abstract). Still others (e.g., Nakamura et al. (of record) and Wen et al. (of record)) have shown that BMP-2 acts to suppress the growth of gastric and brain cancer cells.

Accordingly, given that the role of BMP-2 in cancer has not yet been fully characterized, and contrary to the implications of the data disclosed in the instant application, most reports suggest that its role is to inhibit tumorigenesis, the skilled artisan could not use the claimed invention without undue experimentation. It is not clear that the inhibiting an activity of BMP-2 should be reasonably expected to be therapeutic in the treatment of cancer.

Applicant has again argued that their use of human A549 mouse xenografts for evaluating the therapeutic efficacy of administering to a human an inhibitor of BMP-2 activity that comprises noggin humans should be sufficient to have enabled the skilled artisan to use the claimed invention as of the filing date sought by Applicant. Supporting this argument, Applicant has cited Sirotnak et al. and Meric et al. However it is submitted that Applicant's argument is, at best, anecdotal, as the references cited in the preceding Office action (i.e., Schuh; Bibby; and Peterson et al.) indicate, while such a model has been utilized to evaluate and predict the therapeutic efficacy of treating humans using experimental drugs, its use should not be considered sufficient to show that the claimed invention can be used without undue or unreasonable experimentation; and due to poor extrapolation of the results, their use to accurately and reliably predict the effectiveness of treating humans with the same agent or regimen is limited.

It is further noted that Gura and Bergers et al. (both of record; cited in the first Office action mailed April 27, 2005) address the common lack of extrapolation of the results of studies performed *in vivo* using mouse models to accurately and reliably predict the effects of the same treatments of human patients. As a consequence of such poor extrapolation, Gura teaches studies using mouse models often lead development of good mouse drugs rather than good human drugs, and Bergers et al. suggests careful evaluation of the effects of therapeutic agents in humans before transitioning from preclinical studies to clinical application.

In addition, Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

As noted in preceding Office action, Gura (of record) teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

With further regard to the predictive value of various different preclinical models, Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Most recently, Dennis (*Nature*. 2006 Aug 7; **442**: 739-741) reports, despite their present indispensableness, mouse models, such as xenografts, have only limited utility in predicting the clinical effectiveness of anticancer treatments; see entire document (e.g., page 739, column 2). Dennis explains there is a "laundry list" of problems associated with the use of mice to model human diseases, such as cancer (page 739, column 1). Accordingly, Dennis reports, "[a]lthough virtually every successful cancer drug on the market will have undergone xenograft testing, many more that show positive results in mice have had little or no effect on humans, possibly because the human tumours are growing in a foreign environment" (page 740, column 1). Therefore, quoting Howard Fine, Dennis concludes: " 'Mice are valuable but they are, after all, still mice' ", suggesting the best study subject will always be the human (page 741, column 3).

Thus, taken collectively, it is submitted that there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not

enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

In further response to Applicant's argument, it is again noted that Figure 10, which depicts the results of the experiment described at page 58 of the specification, does not serve as "working exemplification" of the claimed invention, since it merely shows reducing the growth and vascularization of lung cancer cells by subcutaneously co-injecting tumor cells and mouse noggin into a mouse. Instead, the figure shows the incidence of reduced tumor vascularization in mice treated with noggin, as compared to tumor vascularization in mice not so treated. The claims, however, are directed to a method for treating any tumor that overexpressed BMP-2 by reducing its vascularization by a process comprising administering to a subject a therapeutically effective amount of an inhibitor of BMP-2 activity that comprises noggin. As such the claims are directed to a method for treating pre-established tumors in humans. The specification does not exemplify the use of the claimed invention to reduce tumor vascularization and thereby treat the tumor, as it would be expected in its practice were it deemed enabled by its disclosure. As explained in the preceding Office action, the claimed invention cannot be practiced in the "real world" by co-injecting the polypeptide to which the claims refer (e.g., noggin) together with the tumor cells to be treated in a patient.

Additionally, the claims are directed to processes comprising administering to a subject a member of a *genus* of inhibitors of BMP-2 activity that comprise noggin. For example, such inhibitors of BMP-2 activity comprising noggin may comprise the polypeptide of SEQ ID NO: 4 (i.e., human noggin); and yet the specification merely teaches coinjecting lung cancer cells with the polypeptide of SEQ ID NO: 2 (i.e., mouse noggin). The fact that mouse noggin may reduce the growth and vascularization of lung tumors in immunocompromised mice should not be considered a reasonable showing that an inhibitor of BMP-2 activity comprising noggin is also capable of inhibiting growth and vascularization of any other type of tumor, even if BMP-2 is overexpressed. Again, as taught by Ghosh-Choudhury et al. (of record), for example, the role of BMP-2 in other types of cancer (e.g., breast cancer) appears to be to suppress tumorigenesis; accordingly, inhibiting its activity by administering an inhibitor comprising noggin would

therefore not be expected to provide therapeutic benefit. Accordingly, the skilled artisan could not use the claimed invention without undue and unreasonable experimentation.

Now, most recently, Langenfeld et al. (*Oncogene*. 2006; **25**: 685-692) have disclosed that forced expression of BMP-2 in A549 cells significantly enhanced tumor formation in the lungs of mice following their intravenous injection, but did not affect the formation of subcutaneous tumors; see entire document (e.g., the abstract). As discussed above, the specification teaches relatively decreased vascularization of tumors formed by A549 cells following their subcutaneous injection into a mouse in the presence of mouse noggin, as compared to the vascularization of tumors formed by the cells in the absence of noggin. If, as Langenfeld et al. (2006) teaches, BMP-2 less effectively stimulates the growth of subcutaneous tumors, as compared to tumors formed in the lungs, it would seem the projected effects of noggin upon the growth of lung tumors, as determined using the exemplary subcutaneous mouse model described in the specification, are likely exaggerated, since BMP-2 more robustly promotes tumorigenesis in the lungs, as opposed to under the skin, where notably human tumors rarely form (see Langenfeld et al. (2006) at page 690, column 1). At any rate, because Langenfeld et al. teaches the biological effects of BMP-2 upon tumorigenesis vary substantially depending upon the tumor cell's local anatomical environment (see, e.g., the abstract), it is again submitted that the example provided in the specification cannot be regarded as reasonably enabling of the claimed invention, which is method for treating lung tumors, not subcutaneous tumors. Moreover, the results discussed by Langenfeld et al. suggest the mouse model used by Applicant may not be as appropriate as Applicant's remarks would perhaps indicate.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
September 7, 2006